Topics in Primary Care Medicine

Orthostatic Hypotension

MAJ KURT KROENKE, MC, USA, *San Antonio, Texas*

"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

BERNARD LO, MD
STEPHEN J. McPHEE, MD
Series' Editors

Hypertension, from diagnosis to treatment, is a fairly well-defined medical entity. Hypotension is a hazier issue. There is first a considerable number of people whose low blood pressure represents but one end of a bell-shaped curve. With systolic pressures ranging from 80 to 110 mm of mercury and, without symptoms, they can be reassured of a normal if not lengthened life expectancy. At the other extreme is shock, a medical emergency characterized by pressures insufficient to perfuse vital organs. A less critical but quite common clinical problem is that of orthostatic hypotension, wherein the decline in blood pressure is elicited by the assumption of an upright posture. A practical approach to its etiology, diagnosis and treatment is presented.

Physiology

Due to gravitational forces, standing would invariably produce a decline in blood pressure and cerebral perfusion were it not for a homeostatic chain of events. Pooling of blood in the legs leads to a transient drop in cardiac output and, consequently, blood pressure. Simultaneously, however, baroreceptors in the aorta and carotid bodies sense this drop and send a message centrally. Reflex sympathetic stimulation results in cardioacceleration and both venous and arterial constriction. The augmented venous return and increased heart rate boost the cardiac output, which, combined with higher peripheral vascular resistance, returns the blood pressure towards baseline. In a normal person, this happens quickly without symptoms of major sphygmomanometric perturbations.

In actuality, minor changes can occur. With standing, the systolic pressure tends to fall, the pulse quickens and the diastolic pressure remains unchanged or rises slightly. There are, however, no agreed-upon normal limits. Averages from the literature would suggest that a drop in systolic pressure of as much as 20 mm of mercury, a decline in diastolic pressure of 10 mm of mercury and a rise in pulse rate of 20 beats per minute could be considered normal—a rule of "20-10-20." Some authors suggest that a drop of as much as 30/15 mm of mercury may be normal; however, others feel that *any* drop in diastolic pressure is abnormal. More important is the occurrence of symptoms, typically dizziness, attendant upon decreased cerebral perfusion. It is this dyad of an objective drop in blood pressure coupled with subjective light-headedness that produces the disease, orthostatic hypotension. Dizziness is the most common complaint; however, angina, blurred vision, nausea and syncope may occur. Symptoms are frequently worse in the early morning and following meals, the latter due to splanchnic diversion of blood flow.

Etiology

The major causes of orthostatic hypotension are outlined in Table 1. Patients with volume depletion often present with orthostatic hypotension and, if recognized, are the most treatable group. Hypovolemia due to gastrointestinal losses or sweating or bleeding becomes apparent on a careful history taking and physical examination. More subtle is the volume depletion stemming from mineralocorticoid deficiency. Though uncommon, Addison's disease should be considered in unexplained cases. The other major treatable cause of orthostatic hypotension is that related to drugs. Though most drugs listed in the *Physician's Desk Reference* are reported to cause dizziness, the major offenders are psychotropic and cardiovascular drugs. There are differences within categories. Among antihypertensives in common use, methyldopa, prazosin hydrochloride, clonidine and diuretics require particular caution. Among tricyclic antidepressants, imipramine hydrochloride causes frequent orthostasis, whereas nortriptyline hydrochloride may be better tolerated.

Neurologic disease usually works through a common pathway of autonomic dysfunction. In rare cases, central ner-

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From the General Medicine Service, Department of Medicine, Brooke Army Medical Center, San Antonio, Texas.
The views expressed herein are those of the author and do not necessarily reflect the views of the US Army or the Department of Defense.
Reprint requests to Kurt Kroenke, MD, Box 523, Beach Pavilion, Fort Houston, TX 78234.

vous system or spinal cord pathologic conditions, such as strokes, tumors or trauma, underlie the hypotension. More commonly, the mechanism is a peripheral neuropathy, usually diabetes, but on occasion the neuropathy of alcoholism, amyloidosis or uremia. Sometimes the autonomic system alone goes awry. Primary autonomic failure can occur as a central or preganglionic type (Shy-Drager syndrome) and a peripheral or postganglionic form. The preganglionic form has also been called multiple systems atrophy because of the eventual development of central nervous system signs such as corticospinal, cranial nerve, extrapyramidal and cerebellar abnormalities. Both this and the peripheral variant, idiopathic orthostatic hypotension, have been extensively reviewed in the literature. The rise in plasma norepinephrine levels that occurs in normal persons on standing fails to occur in cases of either multiple systems atrophy or idiopathic orthostatic hypotension. In multiple systems atrophy this is presumed due to a failure in central regulation and in idiopathic orthostatic hypotension to an actual depletion of catecholamine stores or degeneration of nerve terminals.

TABLE 1.—*Major Causes of Orthostatic Hypotension*

- Volume Depletion
  - Extrarenal losses (hemorrhage, gastrointestinal losses, sweating and so forth)
  - Mineralocorticoid deficiency (Addison's disease)
- Drugs
  - Psychotropic (tricyclics, phenothiazines, sedatives, narcotics, levodopa)
  - Cardiovascular (antihypertensives, calcium channel blockers, nitrates)
- Neurogenic
  - Peripheral neuropathy (diabetes, alcoholism, uremia, Guillain-Barré syndrome, amyloidosis and the like)
  - Primary autonomic failure
    - Central—multiple systems atrophy (Shy-Drager syndrome)
    - Peripheral—idiopathic orthostatic hypotension
  - Central nervous system or spinal cord disease (strokes, tumors, trauma)—rare
- Miscellaneous
  - Aging
  - Deconditioning (prolonged bed rest, space flight)
  - Pooling (pregnancy, varicose veins, vena caval obstruction)
  - Vasodilatation (intense exertion, heat exhaustion, fever)
  - Sympathicotonia (mitral valve prolapse, some cases of diabetes)

TABLE 2.—*Workup of Patients With Orthostatic Hypotension*

Routine Evaluation	*Additional Tests*
Document orthostasis	
Drug history	
Detect hypovolemia	
History (fluid loss, bleeding, thirst)	ACTH stimulation test
Physical factors (standing pulse increased, mucous membranes, stool Hemoccult)	
Laboratory studies (urine specific gravity and protein; blood urea nitrogen and creatinine; serum sodium and albumin)	
Assess neurologically	
Peripheral	
Physical factors (vibratory sensation, reflexes)	Nerve conduction studies
	Hemoglobin A_{1C}
Laboratory studies (blood glucose)	Rectal biopsy
Autonomic	
History (incontinence, impotence, anhidrosis)	Cold pressor test
	Plasma norepinephrine level
Physical factors (standing pulse not increased, Valsalva)	
Central	
Physical examination (corticospinal, cranial nerves, extrapyramidal, cerebellar)	Computed tomographic scan (if CNS signs on exam)
Consider miscellaneous causes	
History (aging, bedridden, exertion, heat)	
Physical factors (pregnancy, varicosities, mitral valve prolapse)	Echocardiogram

ACTH = adrenocorticotropic hormone, CNS = central nervous system

Miscellaneous causes include aging, deconditioning, pooling, vasodilatation and sympathicotonia. Among persons older than 65 years, 10% to 24% have at least a 20-mm-of-mercury drop in systolic pressure with standing. Deconditioning refers to the baroreceptor disuse that may occur in settings such as prolonged bed rest and space flight. Pooling stems from the impedance to venous return found in conditions such as pregnancy, varicose veins and vena caval obstruction. Vasodilatation that accompanies strenuous exertion, heat exhaustion and fever may produce orthostasis. Sympathicotonia is a poorly understood entity of altered autonomic function characterized by decreased parasympathetic or increased sympathetic tone, or both. This has been postulated as a cause of the orthostatic hypotension that may occur in 10% to 15% of patients with mitral valve prolapse, supported by the improvement in their orthostasis with β-blocker therapy. A similar hyperadrenergic state may produce orthostasis in certain patients with diabetes mellitus, although hypoadrenergic hypotension due to peripheral neuropathy is more common.

Diagnosis

The workup consists of documenting orthostatic hypotension, checking for treatable causes and doing a careful neurologic examination (Table 2).

Authors differ as to the best means of determining orthostatic changes in blood pressure. The pressure should probably be checked after the patient lies supine for several minutes and again after the patient stands for several minutes. Sitting is not enough, unless it produces diagnostic orthostatic changes by itself, or unless the patient is incapable of standing. Ironically, supine hypertension may be prominent, due to compensatory hormonal and volume adjustments mediated in part by the renin-angiotensin-aldosterone axis. A corollary is that before initiating therapy in a patient presumed to have hypertension, standing blood pressures should be determined.

Treatable causes are primarily volume depletion and taking drugs. Detecting hypovolemia due to gastrointestinal losses, sweating or hemorrhage is familiar to most physicians. The uncommon but readily treatable Addison's disease should be pursued with an adrenocorticotropic hormone stimulation test when the findings suggest volume depletion without an obvious cause. Drug taking will be detected by a careful history.

Third, assessing the peripheral, autonomic and central nervous systems is mandatory. Peripheral neuropathies are readily detected on physical examination or, in selected cases,

by nerve conduction studies. If present, the next step is measuring fasting and postprandial blood glucose levels. Glycosylated hemoglobin measurements or a glucose tolerance test can be used to detect less obvious cases of diabetes, although autonomic neuropathy usually occurs in a setting of long-standing, complicated disease. In a nondiabetic person, other causes of peripheral neuropathy must be considered, including alcoholism, amyloidosis and uremia.

Having excluded volume depletion, drugs or a peripheral neuropathy, we should consider a pure failure of the autonomic nervous system. Such patients may also complain of disturbances in bowel, bladder or sexual function or of decreased sweating. Indeed, impotence or incontinence may antedate the onset of orthostasis. Two bedside tests of autonomic function include the heart rate response to standing and that following the Valsalva manuever. Whereas hypovolemic patients have a reflex tachycardia on standing, those with autonomic failure are unable to raise their heart rate. Regarding the Valsalva maneuver, a normal person's pulse rate will rise during the maneuver and decline following it. The normal ratio of maximum pulse during the maneuver to minimum pulse afterwards is 1.25 or greater. A ratio of 1.0 or less is suggestive of autonomic insufficiency. A little more involved but still noninvasive procedure is the cold pressor test, wherein a patient's hand or foot is placed in an ice bath for 60 seconds; normally, the systolic pressure should rise at least 15 mm of mercury.

Should autonomic insufficiency be detected, a full neurologic examination looking for corticospinal, cranial nerve, extrapyramidal or cerebellar signs should be done. This is to separate autonomic failure of the central type (multiple systems atrophy) from the more common peripheral variant (idiopathic orthostatic hypotension). Those with central nervous system symptoms—parkinsonism being the most common—have a worse prognosis, with the average life expectancy following the onset of symptoms being seven years. The more common, purely peripheral form of autonomic neuropathy occurs in middle-aged or older patients, with a 4:1 male predominance. A computed tomographic scan of the head would be indicated primarily in the setting of abnormal findings on a neurologic examination to exclude the rare posterior fossa tumor or infarct causing orthostatic hypotension. Finally, if volume-mediated, pharmacologic and neurogenic mechanisms are excluded, miscellaneous factors such as aging, pooling, deconditioning, vasodilatation and sympathicotonia should be considered.

Treatment

Given an irreversible cause of orthostatic hypotension, therapy consists of prophylaxis, physical methods, volume expansion and vasoactive drugs.

Simple preventive measures begin with avoiding sudden standing. Once upright, flexing the calf muscles or walking to augment venous return is preferable to passive standing. Frequent, small feedings may occasionally be required, with heavier meals inducing significant blood pressure drops due to splanchnic diversion. Strenuous exertion, particularly in hot, humid weather, should be avoided.

Physical measures include elevating the head of the bed 20 to 30 cm (8 to 12 in). This activates the renin-angiotensin system resulting in compensatory volume expansion. Elastic custom-fitted garments can diminish venous pooling but may be subject to considerable variability in patient acceptance. These are not merely support hose, or even knee-high or thigh-length Jobst stockings, but rather graduated pressure garments that allow a gradient of counterpressure to be applied with maximal pressure at the ankles and slight pressure at the top.

Volume expansion begins with a liberal sodium intake of 150 mEq or more per day. Frequently, however, exogenous mineralocorticoids in the form of fludrocortisone (Florinef) acetate must be administered. The starting dose is 0.1 mg per day and may be increased by 0.1 mg per day each week up to 1.0 mg per day. The major complications include supine hypertension, edema, hypokalemia and, in a cardiac patient, congestive heart failure. The goal is not normotension. A standing systolic pressure of 80 to 90 mm of mercury is often sufficient because cerebral perfusion is maintained down to systolic pressures of 70 mm of mercury.

Although the standard of pharmacotherapy, a fludrocortisone regimen alone is frequently insufficient. Other drugs, though experimental and often disappointing, might be needed. Methylphenidate (Ritalin) hydrochloride at a dose of 10 mg one to three times a day may be tried, either alone or in cautious combination with a monoamine-oxidase inhibitor such as tranylcypromine sulfate. With these, the patient should be observed for severe hypertension in the recumbent position. Indomethacin given in doses of 25 to 50 mg three times a day meets with occasional success. Intranasal inhalation of vasopressin just before ambulating has been advocated and vasopressin has the relative advantage of a relatively brief duration of action of one to four hours. In some instances, β-blockers have been useful, particularly in sympathicotonic conditions such as mitral valve prolapse.

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